REMARKS

Claims 15-26 are pending in this application. Support for the amending language of new claims 23-26 may be found in previously filed claims 15-16, and in the specification at paragraph 12. No new matter is added. Reconsideration is respectfully requested in light of the following remarks.

Applicants wish to thank Examiners Dibrino and Chan for extending the courtesy for a personal interview conducted on October 10, 2006, with Applicants' representative Ray Akhavan.

I. Claims 15-22 meet the requirements of 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 15-22 under 35 U.S.C. § 112, first paragraph, as allegedly constituting new matter. More particularly, the Examiner asserts that the limitation "a CD1d blocking antibody" is not supported by the instant application. This rejection is traversed.

The disclosure provides ample support for the limitation "CD1d blocking antibody". Indeed, in the very paragraph in which the Examiner provides to purportedly illustrate the lack of support, there is implicit if not explicit support for the limitation at issue:

> "The originally filed dislcosure is to 'a CD1 blocking agent' that is a molecule that interferes with the binding of a CD1 isoform, such as CD1d, by the TCR, and said agent can be for example, an antibody, a glycolipid, soluble TCR, or soluble CD1." (citations omitted)(emphasis added), (Office Action of July 31, 2006, page 2; hereinafter "Action").

The passage cited above specifically discloses blocking a CD1 isoform, such as CD1d and clearly identifies several agents including an antibody, which may do so. In addition, the Examiner has previously asserted that the instant specification is enabling for "treating pathogenic polyclonal B cell activation or class switching in a patient...comprising administering a CD1 blocking agent that is an antibody... ". (Office Action of February 12, 2003, page 5, section 7). Additional support can be found in original claims 5, 6, 7, 8, 9 or 10 and the specification, e.g., paragraphs 0021-28. Therefore, Applicants respectfully request that this rejection be withdrawn.

II. Claim 22 meets the requirements of 35 U.S.C. § 112, first paragraph

The Examiner asserts that claim 22 allegedly does not adequately describe the scope of the claimed genus, which includes any drug that possesses any immunomodulating activity. In particular, the Examiner asserts that "since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed." (Action, p. 3, paragraph 5). This rejection is traversed.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. Furthermore, it is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991) (citation omitted). Moreover, the examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97

First, it should be noted that claim 22 is method claim that requires administering a CD1d blocking antibody, and where the method further comprises administering an immunomodulating drug. In this regard, all that one of ordinary skill need know is that a drug (e.g., as classified in an index or manual) is immunomodulating. In other words, to satisfy the written description requirement, there is no need to identify each structure for each drug that functions to modulate an immune response or immune system.

Second, the Examiner provides a conclusory statement that the genus is "highly variant". Such a statement without more does not satisfy the Office's burden for showing why an artisan would not recognize that any drug that functions as an immunomodulatory drug is defined by the instant claim. As there is no further clarification provided, it can only be assumed that the Examiner is concerned that one drug can have a different structure as to the next. In this regard, it should be recognized that the structures can and do vary from one drug to the next. However, for the purposes of adequate written description, and as directed to instant claim 22, it is not necessary or even relevant for that matter, that one drug can have a different structure to the next, but only that a drug functions as an immunomodulatory drug (the identities of which are replete in the prior art). In any event, the Examiner does not provide any evidence as to why such drugs, if known as immunomodulatory drugs in the art, are "highly variant", or even explain in what regard such drugs are variant.

The instant disclosure is sufficient in regard to "immunomodulatory drugs" because such drugs are known in the art. An Applicant is not required to describe every detail of the invention that is known in the art. *In re Hayes Microcomputer Products Inc. Patent Litigation*, 982 F2d. 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992). In the instant case, immunomodulatory drugs are known (e.g., disclosed in medical journals/texts/indexes) and thus do not constitute an unpredictable art, or one that is "highly variant". Put another way, whatever the structure of the drug, all must function as immunomodulatory drugs. Indeed, the prior are is replete with publications that utilize the terms "immunomodulatory" in the context of drugs. Thus, one of skill in the art would readily apprehend what is meant by the term "immunomodulatory", and would recognize that describing a host of immunomodulatory drugs in detail would unnecessarily take up page upon page of the instant specification. Moreover, the alleged genus is remarkably small, because the method of claim 22 is limited by the intervening limitations of the base claims (i.e., limited in that a very specific antibody is required in addition to an immunomodulatory drug).

In sum, the specification provides sufficient written description so as to indicate to the artisan that the Applicants are in possession of the claimed invention. It is respectfully submitted that this rejection is improper and should be withdrawn.

III. Claims 15-22 are nonobvious under 35 U.S.C. § 103

The Examiner has rejected claims 15-20 over 5 references (Amano *et al.* in view of Kotzin, Zeng *et al.*, Blumberg *et al.* and Hughes *et al.*) under 35 U.S.C. § 103. This rejection is traversed.

To establish a *prima facie* case of obviousness the prior art references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. Furthermore, there must be some teaching, suggestion or motivation to combine multiple references in constructing an obviousness rejection utilizing multiple references, where such multiple references are individually combined to teach all the claimed limitations.

Applicants respectfully submit that the presently claimed invention is not rendered obvious by the cited prior art. The Examiner has pieced together no less than 5 references to reject claims 15-20. The claims are directed to a method of treatment of lupus in a human patient by administration of CD1d blocking antibodies. Key to the invention is the demonstration that *in vivo* blocking of CD1d by administration of antibody significantly reduces peak levels of serum IgG and IgG anti-dsDNA antibodies, results in delayed proteinuria and prolonged survival.

It would not have been obvious to combine the primary reference Amano *et al.* with one or more of the secondary references cited, because there is both a lack of motivation to do so and a lack of a reasonable expectation of success to target CD1d *in vivo* to effect treatment in a human subject. The proposed rejection is a complicated compilation of selective teachings from the 5 different research articles, but without any specific description of exactly what modifications would have been obvious or why. The Examiner asserts that if would have been obvious and that there would have been a reasonable chance for success, but fails to identify reasons for the combination of references. As such, the Examiner's analysis is built upon hindsight reconstruction of Applicant's invention.

Amano *et al.* (and Zeng *et al.* which is cited therein) provide an absolutely artificial system. In particular, Amano *et al.* (and Zeng *et al.*) are limited to teaching an artificial system, where transgenic animals are genetically modified to express a T cell receptor that recognizes

CD1. In other words, 100% of the cells have a receptor that they would not normally have and which would not occur in a native system, i.e., subject or patient. Therefore, at least as a model system, the Amano *et al.* and Zeng *et al.* do not provide an animal model system that can be suggestive of disease causation, or of successful therapy using a CD1d blocking antibody in a human subject. The transgenic animals do not exhibit any pathogenic polyclonal B cell activation nor evidence of class switching, as the Examiner concedes. Furthermore, the Amano and Zeng models are artificial models that do no reflect what can or would occur in a native system. For example, CD1d is not an antigen for conventional T cells and would not be expected to be present on B cells in a human subject. Rather, such cells are actually restricted to the major histocompatibility antigens by their receptor, which at the time of invention were thought to be involved in SLE etiology.

Furthermore, Amano *et al.* demonstrate a T cell line that is $CD4^-CD8^-$, which expresses Vβ9/Vα4.4 receptor, and which proliferates in response to CD1. The same T cell receptor, when expressed as a transgene, is associated with single positive cells ($CD4^+CD8^-$ or $CD4^-CD8^+$) in one transgenic mouse and with double negative cells ($CD4^-CD8^-$) in another mouse (Zeng *et al.* page 526, last paragraph). Thus, injection of the double negative cells, which correspond to the originally expressed the transgene, were protective of disease, while the single positive cells, which do not correspond to the original cell type, caused a disease phenotype.

In contrast, Applicants show that CD1 reactive cells (NKT cells) are involved in causing lupus and that blocking CD1d effects treatment. NKT cells are present at about 3% of $CD4^+$ T cell populations. (Zeng *et al.* 2003). Furthermore, in contrast to the artificial model provided by the primary reference Amano *et al.* as well as Zeng *et al.*, Applicants show that by administering anti-CD1d antibody onset proteinuria is delayed and survival is prolonged. In sum, Amano *et al.* or Zeng *et al.* do not teach or suggest that NKT cells are causative of disease or that administration of a CD1d antibody can effect the therapeutic effects Applicants teach in the instant application.

One of skill in the art would not find motivation from such demonstrations, to treat a human subject with anti-CD1d antibody, because the artificial system taught by Amano *et al.* and Zeng *et al.* would not occur naturally in an animal or human. Furthermore, even assuming *arguendo* that the combined references suggest that CD1d is implicated in SLE, this does not

amount to teaching or suggesting that blocking CD1d will effect therapy. In other words, under such an extrapolation, the combined references merely provide an invitation for further experimentation. As such there would no expectation of success in treating a human patient with CD1d blocking antibodies, because in a native system (i.e., human patient), only about 3% of T cells are $CD4^+$. At or prior to the time of invention, such NKT cells were believed to be protective and not causative for lupus. (Takeda *et al.* 1993, J. Exp. Med. 177:155). Thus, one would not reasonably have expected that such treatment would result in reduced IgG, anti-dsDNA antibodies, delayed proteinuria and prolonged survival as Applicant have disclosed in the instant specification.

Furthermore, that Zeng *et al.* discusses that 5-6% of T cells are $CD4^+$ only becomes relevant in view of the Applicants' instant disclosure. In other words, to assert that such cells *could* be causative for disease *and* that targeting CD1d would be expected to effect therapy is exemplary hindsight reasoning and accordingly improper. The cited art does not teach or suggest that that CD1d blocking antibody can effect treatment of SLE in a human patient or that any administration of such antibody would be effective for treating SLE in mice or human. Furthermore, the cited art fails to teach or suggest that CD1d expressing B cells are activated by said small population of T cells to cause SLE or suggest any treatment.

With respect to claim 16, pathogenic polyconal B cell activation and class switching refers to autoimmune diseases wherein the primary pathology results from polyclonal stimulation of B cells resulting in overproduction of antibodies, particularly autoantibodies, and more particularly autoantibodies of a pathogenic isotype. The Examiner notes that Amano *et al.* do not teach or suggest the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in systemic erythmatosus lupus (SLE) in a human patient via administration of anti CD1d antibody.

The Examiner asserts that Kotzin teaches that IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing cells, and that that such a process mimics a normal T cell-dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching. Notably, Kotzin fails to teach or suggest an association of CD1 with SLE and clearly does not show the effectiveness of blocking CD1 to treat SLE. Therefore, the rejection over Amano *et al.* (Zeng *et al.*) and Kotzin

fails to establish a *prima facie* case of obviousness, because in the first instances the combined references to do not teach or suggest all the claimed limitations of *treating* a *human* with *CD1d blocking antibody* wherein an effective dose of said antibody *treats* SLE in an *human patient*, or for that matter provide a model predictive or relevant to a human.

Furthermore, Blumberg *et al.* fails to remedy the deficiencies of the foregoing references, because the reference, similarly to all the reference cited, does not teach or suggest that CD1d is expressed on B cells and as a proper target for effecting therapy. As the Examiner points out, the reference discusses CD1c as expressed on B cells, and that CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels. (Action, p. 5, last paragraph). Thus, there is no teaching or suggestion from the combined references that CD1d is causative of SLE via B cell and NKT $CD4^+$ cell interactions leading to pathogenic B cell proliferation or class switching, and importantly, that targeting CD1d results in effective therapy. As such, it is respectfully submitted that claim 16 is nonobvious and the rejection as to claim 16 should be withdrawn.

The combination of references fails to teach or suggest any therapy for SLE, and certainly not the use of an antibody specific to a particular isoform of CD1 – CD1d – for treating lupus. The mere fact that antibodies are utilized of some other disease, autoimmune or otherwise, does not provide adequate suggestion or reasonable expectation for success in their use to treat SLE, as the Examiner implies by using the secondary reference, Hughes *et al.* The selective identification of disparate sections from 5 different research or review articles fails to establish a *prima facie* case of obviousness for the very specific treatment method presently claimed.

Moreover, as to all dependent claims (i.e., 16-22), since the independent claim 15 is nonobvious, all said dependent claims are also nonobvious. See, *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). Withdrawal of the 35 U.S.C. § 103 rejection as to claims 15-20 is respectfully requested.

IV. Claims 21 and 22 are nonobvious under 35 U.S.C. § 103

The Examiner has rejected claims 21 and 22 as obvious over the 5 references cited above, with 2 additional references (Merck Manual, 1992 and Drug Disc. Today, 1998). This rejection is traversed.

The claims require treating a human subject with SLE by administering a CD1d blocking antibody and where said methods for claims 21 and 22 further comprise administration of a second therapeutic agent.

The Examiner only provides interpretations for the Merck Manual, so it can only be assumed that the additional reference is included in error. The Examiner states, "The Merck Manual teaches treatment of SLE with corticosteroid treatment...such as prednisone, in combination with immunosuppressive agents." (Action, page 10, middle paragraph). Interestingly, *any* immunosuppressive agent (e.g., immunomodulatory drug) is apparently deemed obvious.

However, in the first instance, since the Amano *et al.*, Zeng *et al.*, Kotzin, Blumberg *et al.* and Hughes *et al.* references fail to teach all the claimed limitations of claim 15, then claims 21 and 22 are also nonobvious. Therefore, Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-190.

Respectfully submitted,

Date: October 20, 2006

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